American Journal of Medical Genetics (Neuropsychiatric Genetics) 67:53–57 (1996)

Psychiatric Symptoms and CAG Expansion in Huntington's Disease

Maike Weigell-Weber, Werner Schmid, and Roland Spiegel
Institute of Medical Genetics, University of Zürich, Zürich, Switzerland

The mutation responsible for Huntington's disease (HD) is an elongated CAG repeat in the coding region of the IT15 gene. A PCR-based test with high sensitivity and accuracy is now available to identify asymptomatic gene carriers and patients. An inverse correlation between CAG copy number and age at disease onset has been found in a large number of affected individuals. The influence of the CAG repeat expansion on other phenotypic manifestations, especially specific psychiatric symptoms has not been studied intensively.

In order to elucidate this situation we investigated the relation between CAG copy number and distinct psychiatric phenotypes found in 79 HD-patients. None of the four differentiated categories (personality change, psychosis, depression, and nonspecific alterations) showed significant differences in respect to size of the CAG expansion. In addition, no influence of individual sex on psychiatric presentation could be found. On the other hand in patients with personality changes maternal transmission was significantly more frequent compared with all other groups.

Therefore we suggest that clinical severity of psychiatric features in HD is not directly dependent on the size of the dynamic mutation involved. The complex pathogenetic mechanisms leading to psychiatric alterations are still unknown and thus genotyping does not provide information about expected psychiatric symptoms in HD gene carriers. © 1996 Wiley-Liss, Inc.

KEY WORDS: **genotype-phenotype-correlation, unstable trinucleotide repeat, personality change, psychosis, depression**

Received for publication November 28, 1994; revision received May 1, 1995.

Address reprint requests to Roland Spiegel, Institute of Medical Genetics, University of Zürich, Rämistrasse 74, CH-8001 Zürich, Switzerland.

© 1996 Wiley-Liss, Inc.

INTRODUCTION

Huntington's disease (HD) is a rare, autosomal dominantly inherited, neurodegenerative disorder with onset in midlife. The mutation characteristic for HD is an elongated and unstable CAG repeat within the presumptive coding region of the IT15 gene on 4p16.3 [Huntington's Disease Collaborative Research Group, 1993]. Huntington's disease is one of eight disorders, in which unstable trinucleotide repeats were found to be the underlying genetic defects. These mutations are further characterized by the triplet sequence and their localization within or outside the coding region. In HD, as in four other diseases [La Spada et al., 1991; Orr et al., 1993; Koide et al., 1994; Kawaguchi et al., 1994], an expanded CAG repeat eventually leads to an elongated stretch of glutamine residues in the respective proteins. Molecular analysis of the CAG repeat numbers reveals an overlap between normal (8 to 38) and expanded HD alleles (35 to >100) [Andrew et al., 1993; Barron et al., 1993; Duyao et al., 1993; Snell et al., 1993]. Repeats in the intermediate size range (30 to 38 copies) exhibit a low or moderate meiotic instability and have been shown to be a source for new mutations [Goldberg et al., 1993; Myers et al., 1993]. The highest intergenerational instability is observed in expanded CAG alleles, whereas normal alleles are highly stable [MacDonald et al., 1993; Trottier et al., 1994; Zühlke et al., 1993]. Mitotic repeat instability seems to be size dependent and may be the cause for somatic variation found in certain areas of the brain [Telenius et al., 1994]. Symptomatology in Huntington's disease is broad [Harper, 1991]. Important neurological features include chorea and rigidity. Whereas chorea is present in 90% of all adult patients, rigidity especially occurs in patients with juvenile onset (<20 years) [Hayden, 1981].

Psychiatric manifestations are frequent. Minimal psychic changes such as lack of initiative and apathy are seen in almost every patient. Irritability, altered personality, and dementia are common features [Harper, 1991]. In a subset of patients the psychiatric picture can strongly resemble schizophrenia or a major affective disorder [Garron, 1973; Folstein et al., 1983].

Several recent studies have shown a strong inverse correlation, especially pronounced in juvenile cases [Telenius et al., 1993], between CAG repeat length on HD chromosomes, and age at disease onset [Andrew et al., 1993; Duyao et al., 1993; Snell et al., 1993]. On

the other hand no apparent relationship was established between clinical manifestation [Andrew et al., 1993, MacMillan et al., 1993] or velocity of progression [Kieburtz et al., 1994] of the disease and repeat copy number.

The objective of this study was to evaluate possible influences of CAG-repeat length, individual sex, and parental transmission of the genetic defect on the type of psychiatric presentation, which would have an impact on genetic counselling and on long-term psychological care of patients and families.

PATIENTS, MATERIAL, AND METHODS

Patients

Seventy-nine patients from 52 unrelated families were investigated. Juvenile cases were not considered in this analysis. There were 30 men and 49 women, aged 29 to 82 years. Age of onset varied from 26 to 70 years with a mean of 44.2 years, while duration of illness ranged from less than 1 to 24 years. Blood samples and informed consent of patients were obtained for predictive testing of unaffected relatives at risk by linkage analysis and, since 1993, for molecular confirmation of diagnosis in affected individuals.

Psychiatric Classification

Clinical information was obtained from psychiatric (n = 38), neurological (n = 20), both (n = 3) or other (n = 3) records, and by interviewing patients (n = 6) and relatives (n = 14). The patients were grouped according to their relevant psychiatric symptoms into three classes, adapting criteria of DSM-III and DSM-III-R for organically caused psychic syndromes [American Psychiatric Association, 1980, 1987]. These categories were *personality changes*, *depressions*, and *psychoses* (for details see Table I). Symptoms were scored as present if they were observed at any time during the illness. Patients who exhibited more than one psychiatric symptom were categorized according to the most severe symptom and the presence of additional features (see Table I). Patients, who either did not exhibit psychiatric symptoms, or who could not be classified unequivocally, were referred to as *nonspecific alterations*.

Molecular Analysis

DNA was extracted from peripheral leucocytes using standard techniques [Sambrook et al., 1989]. CAG-repeats were amplified by PCR using flanking primers [Riess et al., 1993]. Reaction conditions were 50–100 ng genomic DNA, 10% DMSO, 0.05 Unit Perfect Match (Stratagene), 10 mM Tris HCL, 50 mM KCL, 0.01% gelatine, 0.75 mM $MgCl_2$, 200 μM of each dNTP, 2.5 mCi ^{32}P-CTP, 3.6 pMol of each primer, and 0.4 Unit Ampli Taq DNA polymerase^R in a total volume of 10 μl. Cycling conditions were initial denaturation at 94°C for 2 min followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 50°C for 30 s, synthesis at 72°C for 1 min with a final elongation at 72°C for 5 min. PCR products were resolved on 6% denaturing polyacrylamide gels. Exact CAG copy number was determined by comparison to a M13-sequence ladder.

RESULTS

Fifty patients (63.3%) exhibited characteristic psychiatric symptoms and could be classified in one of the three DSM-adapted categories (see Table I). The remaining patients (n = 29; 36.7%) did not show typical features and therefore were considered to belong to the "nonspecific" group. Ten patients showed psychotic symptoms. In seven of these patients psychotic symptoms definitely preceded choreatic movements and in some of them schizophrenia was assumed; 12 individuals, of whom 3 attempted suicide, were affected by severe depression. The largest group contained 28 subjects with personality changes, mainly emotional instability, irritability and aggression (see Table II).

Sixty-two percent of the patients were females, who were slightly overrepresented in the classes with nonspecific alterations (65.5%) and depression (66.7%). Interestingly, males represented 42.9% of patients with personality changes and 40% of patients with psychoses, although they made up only 38% of the entire cohort (Table II). Statistical analysis, however, revealed no significant differences in sex among the categories (chi^2 test: chi^2 = 0.6; P = 0.9054). Sex of the transmitting parent was known in 83.5% (n = 66) of the patients (see Table II). The disease was transmitted paternally in 32 cases and maternally in 34 cases, respectively. The only group in which maternal transmission occurred more often included patients with personality changes (16 versus 6 patients). In the three other classes the number of paternal transmissions was higher. The influence of parental sex on expression of a specific psychiatric phenotype in general is not significant (chi^2 = 7.3; P = 0.2931). However, parental transmission between patients with personality changes and all other patients is significantly different (chi^2 = 6.6; P = 0.0377). When the different categories were com-

TABLE I. Psychiatric Categories; Classification Criteria

	Personality change	Depression	Psychosis
Characteristic feature(s)	Extraordinary change in behavior or personality	Depressive mood	Hallucinations Delusions
Additional features	Emotional instability Apathy, indifference Distrust Paranoid imaginations Excessive hate Hysteric behavior	Loss of appetite Sleep disturbance Psychomotoric agitation or inhibition Loss of interest and initiative	

TABLE II. Individual Sex and Parental Transmission of HD Mutation in Different Psychiatric Categories

		Sex		Transmission	
Categories	n (%)	Male	Female	Paternal	Maternal
Nonspecific alterations	29 (36.7)	10 (12.6)	19 (24.1)	14 (21.2)	11 (16.7)
Personality change	28 (35.4)	12 (15.2)	16 (20.2)	6 (9.1)	16 (24.2)
Psychosis	10 (12.7)	4 (5.1)	6 (7.6)	5 (7.6)	4 (6.1)
Depression	12 (15.2)	4 (5.1)	8 (10.1)	7 (10.6)	3 (4.5)
Total number (%)	79 (100)	30 (38)	49 (62)	32 (48.5)	34 (51.5)

pared according to age at onset, no differences were found (data not shown). The individual onset-ages showed an equal distribution spanning from 32 to 56 years in each category. One patient with personality changes became ill at 70 years, which was the highest observed onset age. The patient with the earliest age at onset (26 years) presented with psychotic symptoms.

CAG copy numbers in this study ranged from 11–28 for normal alleles and 39–53 for HD alleles, clearly in expanded range (see Fig. 1). The groups, defined by different psychiatric symptoms, did not differ according to CAG-repeat length on HD chromosomes as shown in Figure 1. Since median (44–44.5), mean (44–45.2), and modal value (44) of CAG repeat lengths were almost identical in each class, normal distributions are obvious. All groups exhibited moderate repeat length variation. Depressive patients showed the smallest spectrum (42 to 50 CAG), whilst the broadest range (39 to 53 CAG) was observed in patients with nonspecific alterations. The relation between any psychiatric category and CAG repeat length on HD chromosomes was statistically not significant (F-test: $F = 0.6$; $P = 0.6461$). Furthermore, the distribution of CAG repeat lengths in patients with specific psychiatric symptoms did not differ significantly from those with nonspecific psychiatric changes. Additionally, there was no significant relation between CAG repeat length on normal chromosomes and any psychiatric phenotype (F-test: $F = 1.2$; $P = 0.3011$).

DISCUSSION

Genotype-phenotype correlations have been described for all diseases that are caused by dynamic mutations, with the most striking correlation existing between trinucleotide copy number and age at onset. In myotonic dystrophy the size of the repeat is related not only to age at onset, but also to clinical severity [Harley et al., 1993]. In Kennedy disease there is also a correlation between repeat length and stair-climbing ability [La Spada et al., 1992]. An inverse correlation between CAG copy number and disease onset-age has constantly been described in Huntington's disease [Andrew et al., 1993; Duyao et al., 1993; Norremolle et al., 1993; Novelletto et al., 1994; Snell et al., 1993; Stine et al., 1993]. A smaller, but significant, correlation was also found between CAG repeat length and age of death [Andrew et al., 1993]; however, no such relationship was evident for the rate of clinical decline as shown in a recent study [Kieburtz et al., 1994].

Only two previous investigations focused in part on the effect of the CAG expansion on differing expression of psychiatric features in HD-patients. One study differentiated patients with chorea, psychiatric disturbance (psychosis or depression), dementia, or rigidity as the major presenting feature at the time of diagnosis [Andrew et al., 1993]. In the second study patients were either classified according to their presenting symptoms as psychiatric (cognitive) or motoric (chorea). A third group in this study included rigid juvenile cases [MacMillan et al., 1993]. With the exception of this last group, where patients had considerably greater number of repeats, the different classes in both studies did not differ significantly in respect to CAG copy numbers.

The intention of our study was to further elucidate possible influences of CAG repeat length, individual sex, and parental transmission of the mutation on the type of psychiatric presentation.

Complementary to the findings mentioned earlier [Andrew et al., 1993; MacMillan et al., 1993] our results disclosed no significant relation between any clinical psychiatric phenotype and CAG repeat length. Mean and median of CAG repeat length in all our categories differed no more than four repeats from those observed in total cohorts [Andrew et al., 1993; Duyao et al., 1993; Snell et al., 1993] as well as in clinical subtypes [MacMillan et al., 1993]. In two studies with over 250 schizophrenic patients only one case with CAG-expansion was found [Kremer et al., 1994; St. Clair, 1994]. This was a female, in which schizophrenia without pathological changes in the striatum but temporary "shaking attacks" was associated with CAG expansion in the lower range (CAG = 37). Pure schizophreniform psychosis could therefore represent an extreme form of clinical heterogeneity in HD. We suggest that specific psychiatric features in HD are not a function of CAG copy number alone. Possibly, nondetectable somatic variation in CAG repeat length in specific brain areas could explain the differences in symptoms [Telenius et al., 1994]. Additionally, variability of psychiatric phenotypes may be influenced by unknown genetic and environmental factors, as it has been assumed for age at onset. Genetic components that could influence age at onset have already been discussed before the HD-mutation was characterized. They include genetic imprinting [Farrer et al., 1992; Ridley et al., 1991], ageing genes [Farrer et al., 1984], protecting maternal factors [Myers et al., 1982], and impact of the normal allele [Farrer et al., 1993]. Since we did not find a relation between

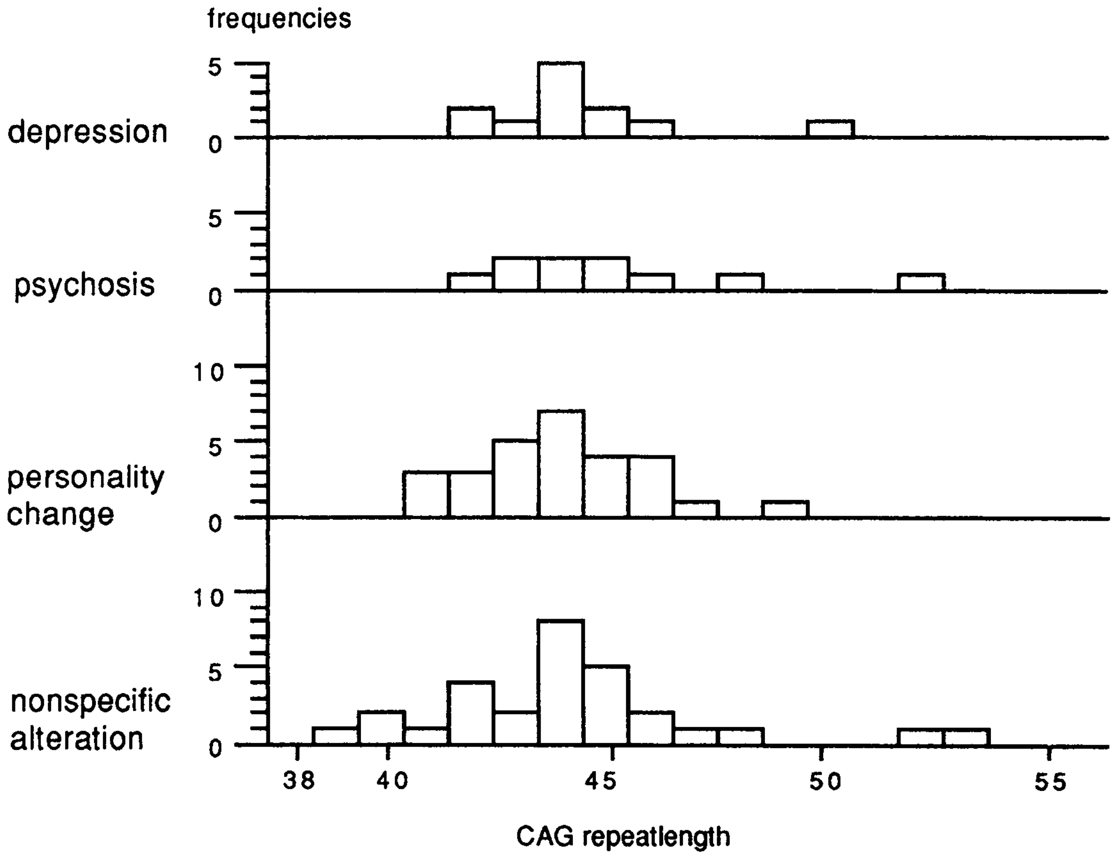

Fig. 1. CAG repeat lengths of HD chromosomes in patients with different psychiatric symptoms, including depression, psychosis, personality change, and nonspecific alterations. Four histograms, demonstrating the distribution of CAG repeat length for each category, are shown. There were similar frequencies and distributions of CAG-expansions for all psychiatric categories, as well as for the group with absent or unspecific changes.

psychiatric phenotype and gender, a marked influence of sex linked genes on psychiatric manifestations in HD can be excluded. Parental origin of the mutation also does not influence symptomatology generally, but in patients with personality changes maternal transmission is significantly higher than in other patients. Therefore genetic imprinting, as well as protecting maternal factors, seem to be unlikely. Psychosocial factors due to illness of the mother could account for the frequent occurrence of personality changes in maternally transmitted cases. Finally, an influence of the normal allele on psychiatric presentation is not obvious.

At present not much is known about the pathophysiological effect of the CAG repeat expansion in neurodegenerative disorders. Comparable repeat lengths and an elongated stretch of glutamin residues in the respective proteins suggest a common pathomechanism. Simple inactivation of the HD gene due to triplet expansion is unlikely, since patients hemizygotic for parts of chromosome 4p show no clinical signs of HD. Homozygotes and heterozygotes for HD exhibit similar clinical features and a gain-of-function mutation was therefore suggested [Wexler et al., 1987; Myers et al., 1989]. At the moment too little is known to exclude similarities in pathology and pathophysiology between psychiatric and neurodegenerative disorders. Unspecific responses to different toxic effects may be part of common pathways leading to psychiatric symptoms.

In conclusion, there is no relation between distinct CAG repeat lengths and specific psychiatric features. Therefore, the size of the CAG-expansion is not a reliable biological marker which could provide information on expected psychiatric symptoms in a HD gene carrier. Nevertheless, in some patients with psychiatric symptoms, e.g., schizophrenia and a positive family history, it might be recommended to investigate the CAG repeat length in the IT15 gene.

ACKNOWLEDGMENTS

We thank all the physicians who helped us in collecting information about patients and our colleagues for support in the lab. We are indebted to Mrs. Cathy Haeberlin for her help in preparing this manuscript.

REFERENCES

American Psychiatric Association (1980): "Diagnostic and Statistical Manual of Mental Disorders" (DSM-III). Washington, DC: American Psychiatric Association.

American Psychiatric Association (1987): "Diagnostic and Statistical Manual of Mental Disorders" (DSM-III-R). Washington, DC: American Psychiatric Association.

Andrew SE, Goldberg YP, Kremer B, Telenius H, Theilmann J, Adam S, Starr E, Squitieri F, Lin B, Kalchman MA, Graham RK, Hayden MR (1993): The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nature Genet 4:398–403.

Barron LH, Warner JP, Porteous M, Holloway S, Simpson S, Davidson R, Brock DJH (1993): A study of the Huntington's disease associated trinucleotide repeat in the Scottish population. J Med Genet 30:1003–1007.

Duyao M, Ambrose C, Myers R, Novelletto A, Persichetti F, Frontali M, Folstein S, Ross C, Franz M, Abbott M, Gray J, Conneally P, Young A, Penney J, Hollingsworth Z, Shoulson I, Lazzarini A, Falek A, Koroshetz W, Sax D, Bird E, Vonsattel J, Bonilla E, Alvir J, Bickham Conde J, Cha J-H, Dure L, Gomez F, Ramos M, Sanchez-Ramos J, Snodgrass S, de Young M, Wexler N, Moscowitz C, Penchaszadeh G, MacFarlane H, Anderson M, Jenkins B, Srinidhi J, Barnes G, Gusella J, MacDonald M (1993): Trinucleotide repeat length instability and age of onset in Huntington's disease. Nature Genet 4:387–392.

Farrer LA, Conneally PM, Yu PI (1984): The natural history of Huntington disease: Possible role of "aging genes." Am J Med Genet 18:115–123.

Farrer LA, Cupples LA, Kiely DK, Conneally PM, Myers RH (1992): Inverse relationship between age at onset of Huntington disease and paternal age suggests involvement of genetic imprinting. Am J Hum Genet 50:528–535.

Farrer LA, Cupples LA, Wiater P, Conneally PM, Gusella JF, Myers RH (1993): The normal HD allele, or a closely linked gene influences age at onset of HD. Am J Hum Genet 53:125–130.

Folstein SE, Abbott MH, Chase GA, Jensen BA, Folstein MF (1983): The association of affective disorder with Huntington's disease in a case series and in families. Psych Med 13:537–542.

Garron DC (1973): Huntington's chorea and schizophrenia. Adv Neurol 1:729–734.

Goldberg YP, Kremer B, Andrew SE, Theilmann J, Graham RK, Squitieri F, Telenius H, Adam S, Sajoo A, Starr E, Heiberg A, Wolff G, Hayden MR (1993): Molecular analysis of new mutations for Huntington's disease: intermediate alleles and sex of origin effects. Nature Genet 5:174–179.

Harley GH, Rundle SA, MacMillan JC, Myring J, Brook JD, Crow S, Reardon W, Fenton I, Shaw DJ, Harper PS (1993): Size of the unstable CTG repeat sequence in relation to phenotype and parental transmission in Myotonic dystrophy. Am J Hum Genet 52:1164–1174.

Harper PS (1991): "Huntington's Disease." London: W.B. Saunders.

Hayden MR (1981): "Huntington's Chorea." New York: Springer.

Huntington's Disease Collaborative Research Group (1993): A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72:971–983.

Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S, Kawakami H, Nakamura S, Nishimura M, Akiguchi I, Kimura J, Narumiya S, Kakizuka A (1994): CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nature Genet 8:221–228.

Kieburtz K, MacDonald M, Shih C, Feigin A, Steinberg K, Bordwell K, Zimmerman C, Srinidhi J, Sotack J, Gusella J, Shoulson I (1994): Trinucleotide repeat length and progression of illness in Huntington's disease. J Med Genet 31:872–874.

Koide R, Ikeuchi T, Onodera O, Tanaka H, Igarashi S, Endo K, Takahashi H, Kondo R, Ishikawa A, Hayashi T, Saito M, Tomoda A, Miike T, Naito H, Ikuta F, Tsuji S (1994): Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Nature Genet 6:9–13.

Kremer B, Goldberg P, Andrew SE, Theilman J, Telenius H, Zeisler J, Squitieri F, Lin B, Bassett A, Almqvist E, Bird TD, Hayden MR (1994): A worldwide study of the Huntington's disease mutation. N Engl J Med 330:1401–1406.

La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH (1991): Androgen receptor gene mutations in x-linked spinal and bulbar muscular atrophy. Nature 352:77–79.

La Spada AR, Roling DB, Harding AE, Warner CL, Spiegel R, Hausmanowa-Petrusewicz I, Yee W-C, Fischbeck KH (1992): Meiotic stability and genotype-phenotype correlation of the trinucleotide repeat in x-linked spinal and bulbar muscular atrophy. Nature Genet 2:301–304.

MacDonald ME, Barnes G, Srinidhi J, Duyao MP, Ambrose CM, Myers RH, Gray J, Conneally PM, Young A, Penney J, Shoulson I, Hollingsworth Z, Koroshetz W, Bird E, Vonsattel JP, Bonilla E, Moscowitz C, Penchaszadeh G, Brzustowicz L, Alvir J, Bickham Conde J, Cha J-H, Dure L, Gomez F, Ramos-Arroyo M, Sanchez-Ramos J, Snodgrass SR, de Young M, Wexler NS, MacFarlane H, Anderson MA, Jenkins B, Gusella JF (1993): Gametic but not somatic instability of CAG repeat length in Huntington's disease. J Med Genet 30:982–986.

MacMillan JC, Snell RG, Tyler A, Houlihan GD, Fenton I, Cheadle JP, Lazarou LP, Shaw DJ, Harper PS (1993): Molecular analyses and clinical correlations of the Huntington's disease mutation. Lancet 342:954–958.

Myers RH, Madden JJ, Teague JL, Falek A (1982): Factors related to onset of Huntington disease. Am J Hum Genet 34:481–488.

Myers RH, Leavitt J, Farrer LA, Jagadeesh J, McFarlane H, Mastromauro CA, Mark RJ, Gusella JF (1989): Homozygote for Huntington disease. Am J Hum Genet 45:615–618.

Myers RH, MacDonald ME, Koroshetz WJ, Duyao MP, Ambrose CM, Taylor SAM, Barnes G, Srinidhi J, Lin CS, Whaley WL, Lazzarini AM, Schwarz M, Wolff G, Bird ED, Vonsattel J-PG, Gusella JF (1993): De novo expansion of a $(CAG)_n$ repeat in sporadic Huntington's disease. Nature Genet 5:168–173.

Norremolle A, Riess O, Epplen JT, Fenger K, Hasholt L, Sörensen SA (1993): Trinucleotide repeat elongation in the Huntington gene in Huntington disease patients from 71 Danish families. Hum Mol Genet 2:1475–1476.

Novelletto A, Persichetti F, Sabbadini G, Mandich P, Bellone E, Ajmar F, Pergola M, Del Senno L, MacDonald ME, Gusella JF, Frontali M (1994): Analysis of the trinucleotide repeat expansion in Italian families affected with Huntington disease. Hum Mol Genet 3:93–98.

Orr HT, Chung M-Y, Banfi S, Kwiatkowski TJ, Servadio A, Beaudet AL, McCall AE, Duvick LA, Ranum LP, Zoghbi HY (1993): Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nature Genet 4:221–226.

Ridley RM, Frith CD, Farrer LA, Conneally PM (1991): Patterns of inheritance of the symptoms of Huntington's disease suggestive of an effect of genomic imprinting. J Med Genet 28:224–231.

Riess O, Noerremoelle A, Soerensen SA, Epplen JT (1993): Improved PCR conditions for the stretch of $(CAG)_n$ repeats causing Huntington's disease. Hum Mol Genet 2:637.

Sambrook J, Fritsch EF, Maniatis T (1989): "Molecular cloning." A Laboratory Manual, 2d Ed. Cold Spring Harbor, NY: Cold Spring Harbor Press.

Snell RG, MacMillan JC, Cheadle JP, Fenton I, Lazarou LP, Davies P, MacDonald ME, Gusella JF, Harper PS, Shaw DJ (1993): Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. Nature Genet 4:393–397.

St. Clair D (1994): Expanded CAG trinucleotide repeat of Huntington's disease gene in a patient with schizophrenia and normal striatal histology. J Med Genet 31:658–659.

Stine OC, Pleasant N, Franz ML, Abbott MH, Folstein SE, Ross CA (1993): Correlation between the onset age of Huntington's disease and length of the trinucleotide repeat in IT-15. Hum Mol Genet 2:1547–1549.

Telenius H, Kremer HPH, Theilmann J, Andrew SE, Almqvist E, Anvret M, Greenberg C, Greenberg J, Lucotte G, Squitieri F, Starr E, Goldberg YP, Hayden MR (1993): Molecular analysis of juvenile Huntington disease: The major influence on $(CAG)_n$ repeat length is the sex of the affected parent. Hum Mol Genet 2:1535–1540.

Telenius H, Kremer B, Goldberg YP, Theilman J, Andrew SE, Zeisler J, Adam S, Greenberg C, Ives EJ, Clarke LA, Hayden MR (1994): Somatic and gonadal mosaicism of the Huntington disease gene CAG repeat in brain and sperm. Nature Genet 6:409–414.

Trottier Y, Biancalana V, Mandel J-L (1994): Instability of CAG repeats in Huntington's disease: Relation to parental transmission and age of onset. J Med Genet 31:377–382.

Wexler N, Young AB, Tanzi RE, Travers H, Starosta-Rubinstein S, Penney JB, Snodgrass SR, Shoulson I, Gomez F, Ramos Arroyo MA, Penchaszadeh GK, Moreno H, Gibbons K, Faryniarz A, Hobbs W, Anderson MA, Bonilla E, Conneally PM, Gusella JF (1987): Homozygotes for Huntington's disease. Nature 326:194–197.

Zühlke C, Riess O, Bockel B, Lange H, Thies U (1993): Mitotic stability and meiotic variability of the $(CAG)_n$ repeat in the Huntington disease gene. Hum Mol Genet 12:2063–2067.